Psychological Effects and Metabolism of N,N-diethyltryptamine in Man

STEPHEN SZARA, MD, DSc; LAWRENCE H. ROCKLAND, MD; DAVID ROSENTHAL, PhD; AND JOSEPH H. HANDLON, PhD, WASHINGTON, DC, AND BETHESDA, MD

SIMPLE INDOLE derivatives like the alkylated tryptamines, N,N-dimethyltryptamine (DMT) and N,N-diethyltryptamine (DET), produce psychotogenic-like symptoms similar to lysergic acid diethyemide (LSD) and mescaline.[1-4]

One of the important metabolic pathways of DET has been shown to be by 6-hydroxylation.[5] The known metabolic pathways of DET are summarized in Fig 1.

Other investigators have reported that naturally occurring indole derivatives, ie, tryptamine itself, skatole, melatonin, can also be hydroxylated in the six position.[6-8] This suggests the possibility that this enzyme system might be involved in spontaneously occurring psychoses.

The present study was undertaken to compare the metabolism of DET in a group of chronic schizophrenic patients and in a group of normal volunteers and to correlate the individual rate of DET metabolism with the psychological effects in man.

Methods

Experimental Procedure.—A 1 mg/kg dose of DET was administered intramuscularly to ten normal volunteers and ten chronic schizophrenic patients. The normal volunteers were white men, 20 to 40 years of age, without symptoms of gross mental or physical disease. Family histories were negative for mental illness. All had normal liver and kidney function. They lived at the Clinical Center at Bethesda on a ward identical to the schizophrenic ward and ate an identical diet. Their daily routines were similar to those of the schizophrenic patients.

The schizophrenic patients were also white men, aged 20 to 40, living at the Clinical Center. They were all chronic patients and had been hospitalized for periods ranging from 8 to 20 years. They were free of physical disease, and all had normal liver and kidney functions.

DET was synthesized by one of us (S.S.), and a sterile solution (20 mg/ml) was prepared by the NIH Pharmacy. The drug was administered in a double-blind design known only to the pharmacy; subjects received the drug and placebo one week apart.

The subjects were interviewed two to three days prior to the first experimental procedure. They were told that they would receive an injection "which might make them feel different." At the same time they were scored on the Jarvik-Abramson subjective scale (J-A scale),[9] and the Quantified Psychiatric Mental Status scale (QPMS scale), devised for assessing mental status during a short interview. This scale is based on the standard psychiatric mental status and consists of 16 continua, on each of which the patient is scored. The data are arranged for easy computer processing.[10]

Subjects were tested individually in a partially soundproofed experimental room equipped with a one-way mirror and microphones for recording.

Shortly before 9 AM on the day of the experiment, the subject was again interviewed. Blood pressure, pulse rate, and pupil size were measured. These were repeated at 30, 60, 90, and 120 minutes postinjection in order to follow autonomic changes. The injection of DET, 1 mg/kg, was given by a nurse at 9 AM. Two observers (S.S. and L.H.R.) remained with the subject for 2 to 2½ hours following the injection. Both kept independent continuous notes on their observations and scored the subjects independently on the QPMS scale.

At 30 minutes postinjection, all subjects were scored on the J-A scale and the QPMS scale. Between 60 and 90 minutes postinjection, a battery of psychological tests were administered to the normal volunteers by one of us (D.R.). At 90

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From the National Institute of Mental Health, Clinical Neuropharmacology Research Center, Saint Elizabeth's Hospital, Washington, DC, and Laboratory of Clinical Science and Laboratory of Psychology, National Institute of Mental Health, Bethesda, Md.

Reprint requests to William A. White Bldg, Saint Elizabeth's Hospital, Washington, DC 20032 (Dr. Szara).

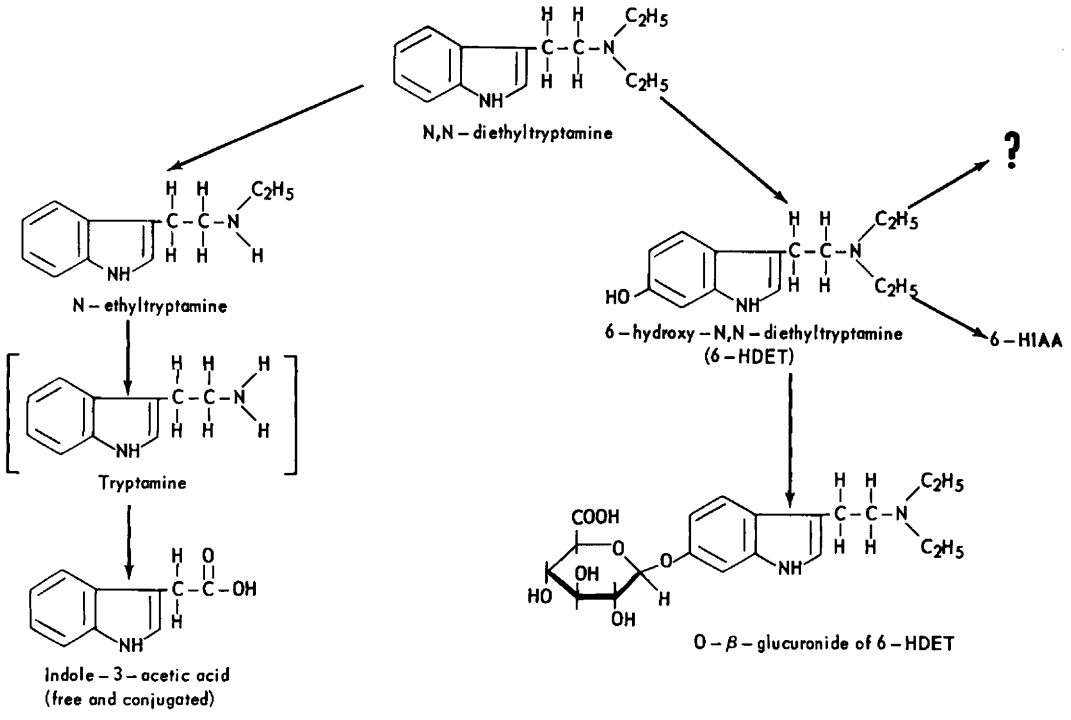

Fig 1.—Metabolism of N,N-diethyltryptamine.

minutes, all subjects were again scored on both scales. All sessions were tape recorded.

On each test day, urine was collected on arising just prior to injection and at three, six, and nine hours postinjection. All specimens were immediately refrigerated and on the following day were sent to the Clinical Neuropharmacology Research Center in a refrigerated container for chemical assay. The chemical determination of 6-hydroxy-N,N-diethyltryptamine (6-HDET) and indole acetic acid was performed by a chemist who was not aware of the drug-placebo and patient-volunteer schedules.

Psychological Evaluation and Testing.—Prior to the experiment, all normal subjects were evaluated psychiatrically by one of us (L.R.), and each received a battery of psychological tests consisting of the Rorschach Ink Blot Test, selected pictures from the Thematic Apperception Test, the Minnesota Multiphasic Personality Inventory, and for some subjects, the Draw-A-Person Test (J.H.).

During the experiment the normal subject took the following tests.

1. Reaction Time (RT): Response was a finger lift from a telegraph key. Warning signal was depression of the key. Three preparatory intervals (PI [2 sec, 10 sec, 2 sec]) were administered in regular sequence, ten trials on each PI.

2. Digit Span: The number series and procedures in Wechsler Adult Intelligence Scale (WAIS) were used.

3. Cross Out A's: Five lines of letters. Subject was instructed to draw a line through each A on the page as quickly as possible.

4. Matching Two 5-Digit Numbers: Subject was instructed to circle "same" or "different" for each pair of numbers and to proceed as quickly as possible.

5. Perspective Illusion: The "test" figure, taken from Gibson [11] consists of two equal-sized cylinders in what appears to be a corridor, the cylinder apparently further down the "corridor" appearing to be larger. There were two "control" figures, each with two cylinders in the same relative position as in the test figure, but with nothing else drawn on the page. On one figure the cylinders were the same size. On the second, the sizes of the cylinders approximated the relative sizes often "seen" on the test figure. The test figure was given twice, once with the instruction to "copy the cylinders as they seem to be, not necessarily as they are"; once with the instruction to "copy the cylinders as they are so that your drawing fits over them exactly, not necessarily as they look." The order of instructions was randomized over subjects. The control figures were presented in randomized sequence between the first and second test figure presentations with the instruction: "Now copy these."

Biochemical Methods.—1. Determination of 6-HDET in Urine: The urine was incubated with bacterial β-glucuronidase and 6-hydroxydiethyltryptamine was extracted into *n*-butanol at pH 9.5. From the butanol the compound was returned into 0.2 *N* acetic acid. This solution was reacted with diazotized ethyl-p-aminobenzoate in 2 *N* hydrochloric acid in order to develop red-colored pigment. After five minutes, this pigment was extracted into chloroform-benzene mixture (3:2 volume per volume [v/v]) at pH 9 after addition of ascorbic acid. Then the pigment was returned into 6 *N* hydrochloric acid and the optical density was measured at 530 mμ on a spectrophotometer. For standard, synthetic 6-HDET was added to water and run through the whole procedure simultane-

TABLE 1.—*Summary of Common Symptoms Occurring in Normal Subjects After Administration of DET*

	Subjects									
	1	2	3	4	5	6	7	8	9	10
1. Nausea & vomiting	3	0	1	1	3	1	3	1	1	3
2. Neurological signs	0	2	0	0	3	3	1	1	0	1
3. Anxiety	1	1	0	1	1	3	3	2	0	1
4. Bizarre somatic complaints	2	2	0	0	2	3	1	1	0	0
5. Visual distortions	1	1	2	1	3	3	3	2	2	3
6. Auditory distortions	1	0	2	0	2	0	0	2	2	3
7. Olfactory distortions	0	0	0	0	2	0	0	0	0	0
8. Paranoid ideation	0	2	0	0	1	3	0	0	1	2
9. Unpleasantness	2	0	0	0	3	3	2	2	0	3
10. Psychological reactions of same subjects to placebo	0	0	0	0	1	—	0	2	1	1

All items (except 1) are qualified on a scale where 0 indicates none; 1, slight; 2, moderate; and 3, marked. Item 1 is rated as different degrees of nausea and a score of 3 was given when vomiting occurred.

ously and served as the basis for calculation. This method is very specific; we obtained zero readings with urine samples collected before administration of the drug. It is sensitive enough to measure as little as 1 μg/ml 6-HDET accurately. The method gives the amount of total 6-HDET. Repeating the procedure without incubation with β-glucuronidase gives the amount of free 6-HDET. The amount of conjugated 6-HDET was calculated.

2. Determination of 3-Indole Acetic Acid: The concentration of indole acetic acid was determined by a slightly modified method of Weissbach et al.[12] This method gives the total indole acetic acid (3-IAA) in the urine. To calculate the amount of 3-IAA derived from the drug, we calculated first the endogenous amount of 3-IAA from the data obtained from the urine collected before the drug and subtracted this from the total obtained in postdrug urine.

Results

Autonomic Reactions and Psychological Responses in Normal Subjects.—The changes produced in man by DET were first noted by Szara[3] and later described in detail by Boszormenyi et al.[4] Because of the significant differences between the results reported by Boszormenyi et al and by us, we will describe our findings somewhat in detail.

In nine out of ten subjects there was an average systolic blood pressure rise of 15.7 mm Hg (range 5 to 30 mm) and an increase in pupil diameter between 1 and 2.5 mm when DET was given. In one subject (case 7) there was a fall of 20 mm Hg in systolic blood pressure. With the placebo there was no significant blood pressure increase, and there was no change in the pupil size.

Table 1 summarizes the most common phenomena observed in normal subjects. The neurological signs varied from slight generalized tremors to gross athetoid movements. Among the bizarre somatic complaints were: "Air is rushing through my body," "My chest is empty and there is a jelly ball in my spine," and "My hands aren't there, my whole body feels funny."

Visual distortions occurred in all subjects and varied from difficulty in focusing and hypersensitivity to light to visual hallucinations perceived as real. Auditory perceptual distortions were much less marked but were present in six subjects. Only one subject had an olfactory hallucination and complained that a glass of water had "a sweetish sickening odor mixed with ammonia smell."*

* This subject (case 5) stated on a subsequent date that he had always been very sensitive to odors. He had been a coal miner and had on four occasions "almost choked to death" from fumes in the mines. At the age of 10 he had witnessed an airplane crash and smelled burning flesh; following this he had vivid nightmares of the incident, including the odor.

TABLE 2.—*Scores Obtained on the Jarvik-Abramson (J-A) Scale and on the Quantified Mental Status (QPMS) Scale in Normal Subjects*

		Subjects									
		1	2	3	4	5	6	7	8	9	10
J-A Scale Total Scores											
Drug	30 min	40	46	65	32	NR	NR	76	76	51	92
	90 min	20	16	5	23	NR	16	32	8	14	14
Placebo	30 min	5	5	3	4	2	—	5	10	4	3
	90 min	4	5	4	8	6	—	3	4	2	1
QPMS Scale Average Scores											
Drug	30 min	14	33	37	24.5	80.5	68	39	23	21	44
	90 min	3.5	17	22.5	23	23	30	28	13.5	12	11.5
Placebo	30 min	3	10	9	7.5	4	—	6.5	8.5	4	7.5
	90 min	3	6.5	10	5.5	3.5	—	5	5.5	4	6

NR indicates the subject was nonratable; and —, no experiment.

TABLE 3.—*Reaction Time in Milliseconds*

PI*	Placebo	Drug	Test	Significance
Initial 2 sec				
$\bar{x}$	169.1	271.7	$t=$ 2.65	0.05
σ	22.7	120.3	$F=$ 28.04	0.01
10 sec				
$\bar{x}$	188.8	348.6	$t=$ 2.03	0.10
σ	21.3	247.4	$F=$135.49	0.01
Second 2 sec				
$\bar{x}$	182.0	318.6	$t=$ 2.80	0.05
σ	24.9	152.1	$F=$ 37.2	0.01

* PI indicates preparatory interval, the time between the warning and the signal to respond.

Five subjects expressed paranoid ideation involving the observers. Two (cases 6 and 10) called the examiners "queers" and made the accusation that "you are trying to seduce me" One (case 9) felt "real suspicious of you two" and another (case 2) said, "My mind is being controlled by you."

The three subjects who found the experience markedly unpleasant were the same subjects who had the most marked rise in blood pressure.

Several other phenomena were characteristic of the reaction but were not included in the above table because of difficulty in quantifying them. All subjects experienced dizziness and increased sweating. Distortions of time sense were commonly described. Loosening of associative thinking was noted by the observers and described by the subjects: "I can't complete my thought: I am thinking and then something else takes over" (case 9).

Wavelike exacerbation of all symptomatology and rapidly shifting levels of awareness were seen in all subjects. "I can't complete my thoughts—I was clear there for a few seconds, my mind is going in and out" (case 9). "I see things—like Frankenstein—it's OK now. I feel clear—oh oh, there I go again, lights are flashing" (case 6).

Subjects also reported occasional synaesthesiae, observing themselves from outside and experiencing opposite feelings simultaneously.

Table 2 tabulates the scores of the J-A (subjective) scale and QPMS scale. Two subjects (cases 5 and 6) were not ratable on the J-A scale because they did not respond meaningfully to the questions. In addition, one of these subjects (case 6) refused to participate in the second test and thus never received placebo.

We have used these scores as a quantitative expression of the intensity of the drug reaction to be correlated with the metabolic data.

Responses in Schizophrenic Subjects.—Physiologic effects were comparable to those noted in normal subjects. Most of the schizophrenic subjects became pale, shaky, and either complained of feeling sick or actually vomited. Several developed tremors or athetosic movements. Six of the ten patients showed an increase in blood pressure of between 10 and 20 mm Hg (one more developed a 65 mm increase in blood pressure). One subject's blood pressure dropped 10 mm Hg, and two were unchanged.

Psychological responses will be described only briefly; most of these subjects could not tell us much of what they were experi-

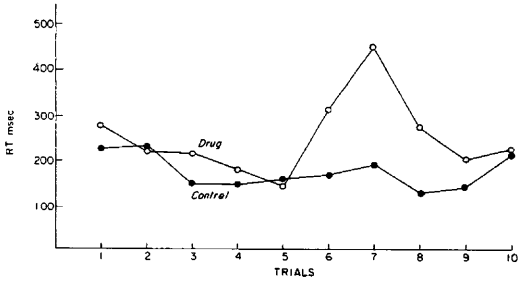

Fig 2.—Reaction times (RT) in the ten trials to the second 2-second preparatory interval in one of the normal subjects (case 1) who showed mild dysleptic phenomena in the drug experiment.

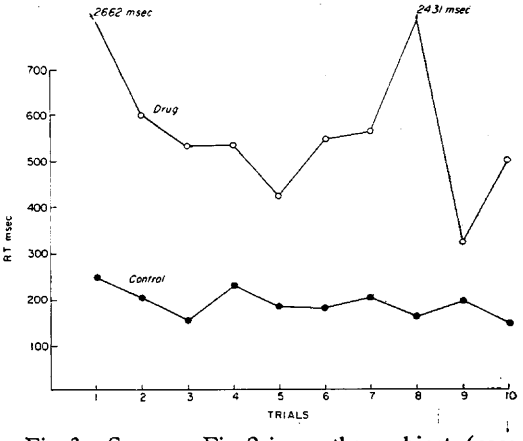

Fig 3.—Same as Fig 2 in another subject (case 6) who experienced severe dysleptic symptoms after DET.

TABLE 4.—*Excretion of Known Metabolites of DET in the Urine of Normal Volunteers (N = 10)*

Metabolite *	% of Administered DET †	
	Average	Range
6-HDET	5.0	2.7- 7.6
3-IAA	12.4	8.3-24.0
Total known	17.4	11.6-28.4
Unaccounted for	82.6	71.6-88.4

* Total (free and conjugated) metabolites excreted in the urine in the nine-hour period following injection.
† DET was administered intramuscularly, 1 mg/kg.

TABLE 5.—*Excretion of 6-HDET by Normal Volunteers: Amount in Urine Collected for Nine Hours After Injection of DET (1 Mg/Kg, Given Intramuscularly)*

Date of Experiment	Patient No.	DET, Mg Administered	6-HDET Excreted & Expressed as % of DET			
			0-3 Hr	3-6 Hr	6-9 Hr	9 Hr Total
1/4/61	1	79.5	1.80	0.82	0.08	2.70
1/11/61	3	61.0	1.50	2.18	0.92	4.60
1/17/61	4	75.0	1.35	0.99	0.43	2.77
2/1/61	5	68.0	2.59	2.34	1.32	6.25
2/6/61	2	58.0	1.59	2.00	0.86	4.45
2/13/61	6	70.4	3.78	3.16	0.66	7.60
2/27/61	7	69.0	1.35	1.70	0.74	3.79
3/8/61	8	72.4	2.94	1.90	1.00	5.84
3/13/61	9	70.3	2.58	1.59	1.33	5.50
3/29/61	10	80.0	2.62	2.45	1.87	6.94
	Average		2.21	1.91	0.92	5.04
	±SD		±0.77	±0.66	±0.49	±1.55

TABLE 6.—*Excretion of 6-HDET by Schizophrenic Patients: Amount in Urine Collected for Nine Hours After Injection of DET (1 Mg/Kg, Given Intramuscularly)*

Date of Experiment	Patient No.	DET, Mg Administered	6-HDET Excreted & Expressed as % of DET			
			0-3 Hr	3-6 Hr	6-9 Hr	9 Hr Total
3/20/61	11	59.6	2.98	4.27	1.45	8.70
4/3/61	12	81.2	1.67	1.72	1.10	4.49
4/5/61	13	83.5	1.53	2.83	1.93	6.29
4/10/61	14	60.0	2.04	2.75	2.54	7.33
4/12/61	15	59.5	2.09	1.93	1.66	5.68
4/19/61	16	61.0	1.39	0.42	1.10	2.91
4/24/61	17	60.0	2.20	2.95	1.24	6.39
4/27/61	18	60.0	0.47	3.04	1.80	5.31
5/1/61	19	60.0	2.39	2.61	1.11	6.11
5/15/61	20	69.0	1.97	2.18	2.94	7.09
	Average		1.87	2.47	1.69	6.03
	±SD		±0.64	±0.96	±0.60	±1.51

encing. Eight of the ten patients showed definite increases in anxiety, while two appeared tranquilized; the "least psychotic" of the patients later described the experience in terms very similar to the accounts of the normal subjects. Three of the schizophrenic men (all diagnosed as chronic paranoid schizophrenic) became more approachable under the drug. They were less defensive, craved physical contact with the observers, and verbalized: "You're my friend," "I love you," "I love my mother and father," and "I am defenseless." The remainder of the patients responded to the drug with behavior which could best be described as exaggerations of their usual ward behavior.

Psychometric Test Results in Normal Volunteers.—It can be seen in Table 3 that RT is impaired by the drug in two ways, ie, both level and variability are increased. (The same effects are found in schizophrenia.) Under both conditions, RT to the second 2-second PI is slower than RT to the first 2-second PI, but the difference is greater (though not significantly) under the drug condition.

The variability between subjects increases under the drug as compared to placebo. This is true for each PI, but most strikingly under the 10-second PI.

Variability within subjects over trials increases markedly under the drug condition as compared with under the placebo condition. To illustrate this phenomenon, Fig 2 and 3 show the wavelike periodic increase of RT to the second 2-second PI for two subjects (cases 1 and 6).

The total time to complete the ten trials takes about 40-60 seconds, depending on subjects. During this period of one minute, there was one to three wavelike increases of RT in most subjects. When all the ten normal subjects were ranked for the average increase of RT to the second 2-second PI, this measure correlated significantly ($P = 0.01$) with both the 30-minute and 90-minute QPMS scale scores under drug, but did not correlate with the J-A scale scores.

Digit Span was adversely affected by the drug. Digits Forward was reduced from 7.4 under the placebo to 6.1 under the drug, $P = 0.10$; Digits Backward, from 5.9 to 3.9, $P = 0.02$; sum of Digits Forward and Digits Backward, from 13.3 to 10.0, $P = 0.05$.

In both the Matching Numbers Test and the Cross Out A's Test, the number of errors made under placebo was small, with a slight,

but not significant, increase occurring under drug. Time to complete the task and variability of group performance were increased markedly, however, in both tests ($P = 0.01$).

In the Perspective Illusion Test, the cylinder on the right is usually seen as larger. The amount of "illusion" may be defined operationally as the difference in size between the right cylinder and the left. Under the placebo, the average illusion effect was about 7 mm for both test figure presentations. Strangely enough, the average effect was 7.9 mm for "as they are," but only 5.9 mm for "as they look," a reversal of the expected direction. Under the drug, the illusion effect tended to increase, but not significantly (in schizophrenic subjects, illusion effects tend, if anything, to decrease). For "as they are," the effect increased from 7.9 to 8.4, but for "as they look," the effect increased from 5.9 to 11.6. The difference does not reach statistical significance. However, for the equal-sized control figure, both cylinders were reproduced as almost exactly the same size under placebo, but under drug, the right cylinder was drawn about 7.6 mm larger than the other on the average, $P = 0.05$. It is as though the initial illusion effect perseverated to this figure under drug. For the unequal size control figure, the relative sizes of the two cylinders approximated the actual relative size almost exactly under both placebo and drug.

Seven measures which were thought to be affected by set or attention were intercorrelated: RT to 2-second PI; RT to 10-second PI; 10-second PI minus 2-second PI; second 2-second PI minus initial 2-second PI; sum of Digits Forward plus Digits Backward; time to Cross Out A's; time to Match Numbers. Of the 21 correlations only one was significant under placebo (median = 0.21), and two under drug (median = 0.35). Subjects were ranked for each measure forming a matrix of seven rankings of ten subjects. A Friedman two-way analysis of variance indicated that subjects differed significantly with respect to these measures under placebo ($\chi^2_r = 22.14$, $P = 0.01$) and under drug ($\chi^2_r = 31.64$, $P = 0.0001$). Kendall's coefficient of concordance indicated that whereas homogeneity of rankings over measures was not statistically significant under the placebo ($W = 0.248$), it was significant under the drug ($W = 0.396$, $P = 0.01$). Thus, subjects seemed to differ initially with respect to a heterogeneous group of measures of set or attention, and the effect of the drug was to accentuate these differences.

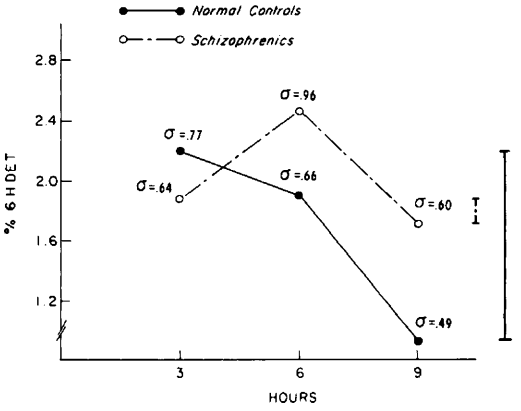

Fig 4.—Excretion of 6-HDET by ten normal and ten schizophrenic subjects. Ordinate: 6-HDET found in the three hourly urine samples and expressed as percent of DET, 1 mg/kg, given intramuscularly. Abscissa: urine collection time after the injection of DET. σ = standard deviations. Total amount collected in the nine-hour period averaged 5.04% for the normal control ($\sigma = 1.55$) and 6.03% for the schizophrenic group ($\sigma = 1.51$). Perpendicular bars on the right show the difference between the percentage values of 6-HDET found in the three hours and nine hours, respectively.

TABLE 7.—*Correlation of Scale Scores and Rank-Ordered Symptomatology With Amount of 6-HDET Excreted by Normal Volunteers*

Items Correlated With 6-HDET Excretion	Correlation Coefficient	Level of Significance
Age	−0.20	NS *
Chronologic order of experiment	+0.65	<0.05
J-A scale		
30 min scores	+0.83	<0.01
30-90 min, average	+0.55	0.10
QPMS scale		
30 min scores	+0.63	<0.05
30-90 min, average	+0.56	0.05<P<0.10
Autonomic changes		
Blood pressure	+0.61	<0.05
Nausea, vomiting	+0.31	NS
Neurological signs	+0.68	<0.05
Perceptual distortions		
Visual	+0.88	<0.01
Auditory	+0.56	0.05<P<0.10
Olfactory and gustatory	+0.39	NS
Proprioceptive	+0.35	NS
Psychological changes		
Paranoid ideation	+0.63	P<0.05
Rush of thoughts	+0.49	NS
Homosexual concerns	+0.69	P<0.05
Anxiety	+0.88	P<0.01

* NS indicates that the correlation was not significant.

Biochemical Results.—Table 4 shows a summary of the metabolic results obtained from the normal volunteers. It can be seen that on the average 5% of the administered DET is found as 6-HDET, free and conjugated, with a range of 2.7% to 7.6%. The average amount of 3-IAA was 12.4% of the administered DET. The total of the known metabolites was 17.4% which leaves about 83% of the drug unaccounted for.

Table 5 shows the individual excretion values in the normal volunteers for each three-hour period postdrug and the nine-hour total excretion period. The major portion of 6-HDET is excreted in the first three-hour period, less in the second three hours, and much less in the third three hours.

Table 6 shows the excretion of 6-HDET by schizophrenic patients. The schizophrenics as a group excreted slightly more 6-HDET in the nine-hour period than the normal group; the difference is not statistically significant ($P = 0.10$). The excretion pattern, however, differs from that of the normal group as is shown in Fig 4. Figure 4 shows that normals excrete more 6-HDET in the first three-hour period than in the second; by contrast, the schizophrenic subjects excrete more in the second three-hour collection period.

To test whether this reversal in slopes is statistically significant, the two groups were compared with respect to these two time periods, using the trend analysis model recommended by Edwards.[13] Neither diagnostic groups nor time periods are significantly different from one another, but the interaction between both primary variables is significant at the 0.05 level, confirming the impression conveyed in Fig 4. The difference between the groups in the third three-hour period is significant at the 0.01 level, the schizophrenics still excreting more 6-HDET than the normal subjects during that time.

Correlations.—The main purpose of the study was to ascertain whether or not a positive correlation exists between the amount of 6-HDET excreted and the intensity and duration of the symptomatology. In the next table (Table 7) the results are presented. In the first column the items that were correlated with 6-HDET excretion are listed. The second column shows the correlation coefficients obtained and the third column indicates the level of significance.

Psychodynamic Considerations.—An attempt was made by one of us (J.H.) with knowledge of the drug reaction to predict from predrug psychiatric and psychological data how subjects might respond to the drug. This attempt was not successful and the details are not presented.†

Comment

The reactions of our subjects to DET are similar to those previously described,[4] but there are significant differences. Boszormenyi et al describe mood changes in the direction of euphoria; their subjects generally enjoyed the drug experience and wished to repeat it. Verbal productions under the drug tended to become mystical and philosophical and following the drug experience "many of the normal experimental subjects showed artistic tendencies which they had not shown before." [14]

By contrast, six of our ten normal volunteers found the DET experience an unpleasant one, three of them markedly so. There was no enthusiasm in the group for a repetition of the experience and several subjects stated emphatically that they would leave the Clinical Center before submitting to it again. We could detect very little that might be called mystical or philosophical in our

† After the details of the subject's reaction were known to all of us, we found that there were three individuals who demonstrated more pathological response than would have been expected from the amount of metabolite extracted, and three individuals who responded less pathologically than would have been expected. The data from the three "over-responders," and from the three "under-responders" were again examined to determine what common features might be found in their personality structure.

The over-responders were of two types: (*a*) those who indicated that they were aware of a great deal of internal conflict, and (*b*) those who had brittle, rigid defenses, with little tolerance for new, ambiguous, and, therefore, threatening experiences.

The under-responders tended to either (*a*) passively yield to the experience, or (*b*) make some attempt to keep intellectual distance from the experiment.

It should not be inferred that the personality patterns described above are the only ones that might be obtained from such a study. Also, it should be emphasized that the above is after the fact, and would certainly need further experimental validation.

subjects' drug reactions and noted no upsurge of artistic inclination following the drug experience.

One difference between the two studies is in the dosage of DET administered. Boszormenyi et al gave 0.70-0.80 mg/kg of body weight; we gave 1.0 mg/kg. The higher dosage may have tended to make the experience less pleasant because of more marked vegetative phenomena. However, in order to attempt to wholly explain the differences, one must look to extradrug factors which can potentially influence the drug response.

The Subject.—The subjects in the Boszormenyi et al study were colleagues of the investigators, other professionals, and artists; ours were unemployed men from an economically depressed mining area. Only one of our subjects had gone beyond high school. As a group they were culturally deprived and there was little interest in introspection, philosophy, music, art, etc. In addition, as Pollin and Perlin [15] have shown, the "normal volunteer" at the Clinical Center cannot be considered as a representative sample of normal population because of the unique factors which motivate individuals to accept such a position.

After the first few subjects had received the drug, the expectations of the remaining subjects were generally negative. They expected an unpleasant experience and looked forward to it with trepidation. This increased tension might have affected the rate of 6-hydroxylation, which in turn was reflected in the correlation found between 6-hydroxylation and the chronological order in which the drug was given. Such a possibility is not unexpected if we consider the considerable effect of epinephrine on microsomal enzyme activity.[16]

The Subject-Investigator Relationship.—The subjects of Boszormenyi et al were, for the most part, friends and colleagues of the investigators; ours were not. During the drug reactions we remained as observers, except to ask questions relevant to the scale scoring and to encourage the subject to verbalize his experiences.

The drug appears to render the subject relatively helpless to control his strange, new environment. He can give in to the experience and enjoy it, or struggle to regain control, find himself unable to do so, and begin to experience panic. We would suggest that the alternative chosen depends intimately on the investigator-subject relationship (as well as on personality factors in the subjects and on the supportiveness of the investigator).

The Investigator.—One of the characteristics of the psychotomimetic drug effect is a greatly heightened suggestibility of the subjects.[17] Therefore we would expect that the behavior, mood, and expectation of the investigator would significantly influence the reaction of the subject. The double-blind procedure of drug administration was chosen to counteract this influence in our subjects.

The Physical Environment.—We administered the drug in a relatively bare, experimental room equipped with chairs, an examining table, one-way mirror, and microphones. We did not play music for the subject nor present other props. Again the information is not available from the Boszormenyi et al paper, but we would expect that any significant change in the physical surroundings would influence the drug reaction.

An interesting and so far unsettled question is to what extent do the clinical changes induced in control subjects by the dysleptic ‡ drugs simulate a schizophrenic psychosis. In our material with DET there is a significant rise in RT level, indicating a general slowing of RT performance. This slowing occurs also on the Matching Numbers and Cross Out A's tests. RT variability, both within and between subjects, also increases. These RT test signs are found characteristically in schizophrenic groups; ie (in schizophrenic subjects, too) the effect of a series of RT trials on a long PI is to increase RTs on a series with a short PI which is given immediately afterward.[18] In our normal subjects with DET, a similar effect occurred, though not significantly for the group as a whole; but this effect did correlate

‡ The word "psycho-dysleptic," or simply "dysleptic," for the class of hallucinogenic or psychotomimetic drugs was first proposed by Jean Delay (in Freyhan, F.A.: On Classifying Psychotropic Pharmaca, *Compr Psychiat* 2:241-247, 1961).

significantly with the extent to which the subjects were affected by the drug.

The latter finding suggests that the subjects respond in different degrees to the drug and that we need to pay attention to individual differences in this regard. For example, the normal volunteers differed under the placebo condition with respect to a number of measures presumed to reflect attentiveness or set, but the effect of the drug was to accentuate these differences. If we draw an analogy with schizophrenia, we might consider that individuals are differentially predisposed to this disorder, either through heredity or life experience, and that in the psychotic state they will manifest different and more varied degrees of clinical severity, depending on the predisposition or premorbid condition.

A very interesting phenomenon was the finding that the RT under drug conditions periodically increased in a wavelike manner. The wavelike appearance of subjective phenomena (distortion of perception, visual hallucinations, etc) was noted in all our subjects. This phenomenon seems to be common to all dysleptic drugs (LSD, psilocin, mescaline) and has been described often by several authors.[19,20] No hypothesis was offered to explain these waves, but it is tempting to speculate that a characteristic wavelike appearance of spiking activity in the hippocampus of cats after administration of dysleptic drugs might be related to this phenomenon.[21] Similar spiking activity as recorded from deep electrodes in the hippocampus of epileptic patients has been shown to be correlated with a brief loss of consciousness, twilight state, dreamy state, and feeling of familiarity or strangeness in the aura phase of the epileptic attack.[22]

The positive correlation between the amount of 6-HDET excreted in the urine and the psychologic, autonomic, and neurologic changes produced in normal volunteers after administration of DET, 1mg/kg, is a striking phenomenon considering the relatively small number of subjects studied. Such a correlation was predicted on the basis of animal behavioral studies with DET and 6-HDET.[5] The differences, however, in the rate of metabolism in the two species are considerable (in man, 17% of the administered DET can be accounted for as metabolites in contrast to the rat where more than 70% is the corresponding figure), indicating the need for further investigation in this area before final conclusions can be drawn about the involvement of 6-hydroxylation in the psychological changes produced by DET.

The delayed excretion curve for 6-HDET in schizophrenic subjects appears to be a clear-cut phenomenon. This delay might be explained by differences in absorption, metabolism, renal clearance, or by some mechanism which inhibits excretion. This mechanism could be a difference in tissue distribution or in specific or nonspecific binding of metabolites. Animal experiments in this area are in progress.

Without question DET is a powerful, short-acting drug which belongs to the group of drugs variously designated as hallucinogenic, psychedelic, psychotomimetic, or dysleptic. These drugs are currently being tested by widely scattered groups to determine their usefulness as an aid to psychotherapy,[19] or as a new form of therapy in psychiatry.[23] The tryptamine derivatives have the unique property of short duration of action which makes them convenient candidates for such purposes. But before they can be recommended for general uses, much more basic work has to be done on the various factors playing a role in their mechanism of action.

Mrs. A. Aikens performed the clinical determination of 6-hydroxy-N,N-diethyltryptamine and indole acetic acid.

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ERRATUM

In the article "Reduction in Symptomatology in Ambulatory Patients," by Drs. Jacobs, Globus, and Heim, published in the July issue of the ARCHIVES, the following correction should be made. On page 48, right-hand column, line nine of the second paragraph, the confidence level should read $P<0.10$, not $P<0.01$.